

# A Rapid Extraction Method to Quantify Drug Uptake in Contact Lenses

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**Purpose:** To develop a simple extraction procedure to quantify the uptake of four topical ocular pharmaceutical drugs into contact lenses (CLs).

**Methods:** Four silicone hydrogel (SH) CLs (balafilcon A, senofilcon A, lotrafilcon B, comfilcon B) and four conventional hydrogel (CH) CLs (nesofilcon A, hilafilcon B, nelfilcon A, etafilcon A) were evaluated. The drugs studied were natamycin, moxifloxacin, timolol maleate, and ketotifen fumarate. For drug incubation, three CLs of each type were placed in 1 mL of 1 mg/mL drug-loading solution for 24 hours. The lenses were then extracted in 2 mL methanol for 2 hours. This process was repeated to obtain a total of three extraction cycles. Detection of natamycin, moxifloxacin, ketotifen fumarate, and timolol maleate were measured by absorbance at 305, 287, 297, and 295 nm, respectively.

**Results:** The majority of the drugs were extracted after the first extraction cycle ( $P < 0.001$ ). For moxifloxacin and timolol, CH CLs had higher drug uptake than SH CLs ( $P < 0.05$ ). There were no differences in drug uptake between CH CLs and SH CLs for natamycin and ketotifen ( $P > 0.05$ ).

**Conclusions:** This study provides a simple approach to determine drug uptake into CLs. This method can also be modified, such as changing the extraction time, extraction cycles, or extraction solvent to better suit other drugs and CL combinations.

**Translational Relevance:** There is considerable interest in using CLs for ocular drug delivery. Accurately quantifying drug uptake on CLs has been a challenge. Hence, this study provides a simple method to quantify drug uptake in CLs.

## Introduction

Over the last decade, there has been considerable interest in using contact lenses (CLs) beyond their intended application in vision correction.<sup>1</sup> One area of research that is rapidly gaining traction is ocular drug delivery using CLs.<sup>1–19</sup> Drug delivery using CLs was conceptualized to address the key problems associated with conventional therapies to treat eye diseases such as glaucoma,<sup>16</sup> infection,<sup>6,10,15</sup> myopia,<sup>17</sup> allergies,<sup>8</sup> and dry eye.<sup>18,19</sup>

Currently, eye drops and ointments account for over 90% of all ophthalmic formulations for ocular drug delivery.<sup>20–23</sup> However, the anatomy of the eye presents several barriers that prevent effective drug delivery via this approach. Factors such as tear dilution,<sup>24</sup> blinking,<sup>24</sup> and nonspecific absorption<sup>20,24</sup>

limits residence time and effective drug penetration through the cornea.<sup>25</sup> To compensate for low drug bioavailability, frequent dosing can be employed with eye drops, but this practice in turn results in problems with patient compliance<sup>26</sup> and overdosing of drugs.<sup>27</sup>

CL drug delivery provides two main advantages over ophthalmic formulations. The first benefit results from the creation of the postlens tear film generated when a CL is placed on the cornea. This physical CL barrier shields the postlens tear layer from the blinking reflex, while also restricting tear mixing and exchange.<sup>28</sup> As a consequence, drugs released into this layer from the CL are trapped and have longer precorneal residence time.<sup>29</sup> The second advantage is the ability to engineer the material properties of a CL in such a way that it provides sustained drug release,<sup>3,19,30</sup> eliminating the need for multiple dosing.

Understanding the interaction between the drug and the CL material is thus essential to optimizing drug delivery. One important property is the drug partition coefficient,<sup>13</sup> which provides an estimate of the concentration of a particular drug in the lens. This information is useful to gauge the effectiveness of a CL material for drug delivery by comparing its drug uptake with its release profile.<sup>13</sup> However, measuring drug uptake into a lens is very difficult. So while there are numerous studies on CL drug delivery, far fewer have reported data on drug uptake.<sup>2-14,31,32</sup>

These studies typically quantify drug uptake into the lens by measuring the concentration of the drug-loading solution at the beginning and the end of the incubation period.<sup>2-13,31,32</sup> The difference in drug concentration is then attributed to the amount of drugs sorbed by the lens.<sup>2-13,31,32</sup> However, there are some inherent problems with this indirect measurement approach. Firstly, drugs may precipitate out of solution, collect at the bottom of the vial, or deposit onto the side of the vials. As a result, over time a decrease in drug concentration may occur that is not attributed to uptake into the CL. Secondly, the concentrations of the drug-loading solutions are many fold higher than the small amounts of drug that are actually absorbed by the lens.<sup>2-14,31,32</sup> Consequently, there are extremely large errors associated with measuring such small changes in concentration in the drug-loading solution.

A more direct approach to measuring CL drug uptake is therefore desired, but very few studies have attempted to quantify drugs in this manner.<sup>14,15</sup> One promising method, by Kakisu et al.,<sup>15</sup> measured the uptake of two antibiotics, gatifloxacin and moxifloxacin, by soaking drug-containing lenses in methanol for 24 hours. This approach is similar to extraction methods commonly used to quantify protein and lipid deposits on CLs.<sup>33-37</sup> To this end, we hypothesize that a modification of this method could be applied to quantify drug uptake on CLs. The purpose of this study is to develop a simple extraction procedure to quantify drug uptake into contemporary CL materials for four commonly used ocular pharmaceutical agents (natamycin, moxifloxacin, timolol maleate, and ketotifen fumarate).

## Materials and Methods

### Lens Preparation

Four commercially available silicone hydrogel (SH) CLs (balafilcon A, Bausch & Lomb, Rochester,

NY; senofilcon A, Johnson & Johnson, Jacksonville, FL; lotrafilcon B, Alcon, Fort Worth, TX; comfilcon B, CooperVision, Pleasanton, CA) and four conventional hydrogel (CH) CLs (nesofilcon A, Bausch & Lomb; hilafilcon B, Bausch & Lomb; nelfilcon A, Alcon; etafilcon A, Johnson & Johnson) were evaluated in the study. All lenses had an 8.6-mm base curve, and -3.00 dioptic power and were obtained from the manufacturer in the original packaging. Tables 1 and 2 detail the properties of the SH and CH CLs, respectively.

Three CLs of each type were removed from their original packaging and placed in 5 mL PBS in a 12-well clear plate (VWR International, Missauga, Ontario, Canada) and gently shaken for 24 hours at room temperature to remove any packaging solution. The lenses were then placed in 1 mL of 1 mg/mL drug-loading solution.

### Drug Incubation Solution

Natamycin, ketotifen fumarate, and timolol maleate were purchased from Sigma-Aldrich Corp. (Oakville, Ontario, Canada), and moxifloxacin was purchased from Selleckchem (Houston, TX). After the initial preparation procedure, the lenses were incubated in 1 mL of 1 mg/mL drug solution in phosphate buffered saline (PBS), pH 7.4, for 24 hours. Studies with natamycin and moxifloxacin were performed in light-minimizing conditions. With the exception of natamycin, which was prepared as a suspension, all other drugs completely dissolved in solution.

### Detection

Detection of natamycin,<sup>3,6</sup> moxifloxacin,<sup>38</sup> ketotifen fumarate,<sup>8</sup> and timolol maleate,<sup>39</sup> was measured at 305, 287, 297, and 295 nm, respectively, in a UV-star 96-well microplate (Greiner Bio-One, Monroe, NC) using a spectrophotometer (SpectraMax M5 UV-Vis; Molecular Devices, Sunnyvale, CA).

### Negative Control

Three lenses of each type were extracted in methanol for 48 hours. After the extraction period, an absorbance spectrum of the lens extracts for each CL was determined between 210 and 350 nm in 1-nm increments. The CL extracts were then evaporated using nitrogen purge for 1 hour. The extracts were resuspended in 250  $\mu$ L methanol, and another absorbance spectrum was determined between 210 and 350 nm.

**Table 1.** Properties of SHs Used in the Study

Properties	Pure Vision 2	Acuvue Oasys	Air Optix Aqua	Biofinity
USAN	Balafilcon A	Senofilcon A	Lotrafilcon B	Comfilcon B
Manufacturer	Bausch & Lomb	Johnson & Johnson	Alcon	CooperVision
Water content, %	36	38	33	48
FDA group	V	V	V	V
Center thickness, mm	0.07	0.07	0.08	0.08
Oxygen permeability ( $\times 10^{-11}$ )	91	103	110	128
Oxygen transmissibility ( $\times 10^{-9}$ )	130	147	138	160
Surface treatment	Plasma oxidation	None	25-nm plasma coating	None
Principal monomers	NVP, TPVC, NVA, PBVC	mPDMS, DMA, HEMA, siloxane macromer, TEGDMA, PVP	DMA, TRIS, siloxane macromer	FM0411M, HOB, IBM, M3U, NVP, TAIC, VMA

USAN, United States adopted name; DMA, *N,N*-di methylacrylamide; FM0411M, *a*-methacryloyloxyethyl imminocarboxyethoxypropylpoly(dimethylsiloxo)-butyldimethylsilane; HEMA, hydroxyethyl methacrylate; HOB, 2-hydroxybutyl methacrylate; IBM, isobornyl methacrylate; MA, methacrylic acid; mPDMS, monofunctional polydimethylsiloxane; NVP, *N*-vinyl pyrrolidone; TEGDMA, tetraethylene glycol dimethacrylate; TPVC, tris-(trimethylsiloxo silyl) propyl vinyl carbamate; TRIS, trimethylsiloxo silane; M3U, *av*-bis(methacryloyloxyethyliminocarboxy ethoxypropyl)-poly(dimethylsiloxane)-poly(trifluoropropylmethylsiloxane)-poly(*v*-methoxy-poly(ethyleneglycol)propyl methylsiloxane); NVA, *N*-vinyl amino acid; PBVC, poly(dimethylsiloxo) di(silylbutanol) bis(vineyl carbamate); PVP, polyvinyl pyrrolidone; TAIC, 1,3,5-triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; VMA, *N*-vinyl-*N*-methylacetamide.

## Standard Curve

A standard curve for each drug was generated by diluting the drug concentrations to a range of 0 to 1 mg/mL in methanol, and only the linear portion was used as the range of detection. The generated curves had a correlation coefficient above 99.5%. The concentration of the drugs in the samples was determined by subtracting the background absorbance of the negative control divided by the slope obtained from the standard curve.

## Extraction Cycles

After the 24-hour drug incubation time, the lenses were removed from their drug-loading solution and air-dried for 10 seconds before being placed into 2 mL methanol extraction solvent. The vials were capped, covered in parafilm to avoid any evaporation, and placed on an orbital shaker at room temperature for 2 hours. After 2 hours, the lenses were removed from their vials and placed in 2 mL fresh methanol. This process was repeated for a total of three extraction cycles.

**Table 2.** Properties of CHs Used in the Study

	Biotrue	SofLens	Dailies AquaComfort Plus	1-Day Acuvue Moist
USAN	Nesofilcon A	Hilafilcon B	Nelfilcon A	Etafilcon A
Manufacturer	Bausch & Lomb	Bausch & Lomb	Alcon	Johnson & Johnson
Water content, %	78	59	69	58
FDA group	II	II	II	IV
Center thickness, mm	0.10	0.10	0.10	0.08
Oxygen permeability ( $\times 10^{-11}$ )	42	22	26	28
Principal monomers	HEMA, NVP	HEMA, NVP	PVA, HPMC, PEG, FMA	HEMA, PVP, MA

FMA, *N*-formylmethyl acrylamide; HPMC, hydroxypropylmethylcellulose; PEG, polyethylene glycol; PVA, polyvinyl alcohol.

**Table 3.** Uptake of Natamycin ( $\mu\text{g}$ ) on SH and CH CLs Incubated in a 1-mg/mL Drug Solution

Commercial Name	Material	Extraction 1, $\mu\text{g}$	Extracted, %	Extraction 2, $\mu\text{g}$	Extraction 3, $\mu\text{g}$	Total, $\mu\text{g}$
<sup>SH</sup> Pure Vision 2	Balafilcon A	193.8 $\pm$ 71.9	99.4 $\pm$ 0.1	0.6 $\pm$ 0.4	0.6 $\pm$ 0.4	195.1 $\pm$ 72.6
<sup>SH</sup> Acuvue Oasys	senofilcon A	157.2 $\pm$ 33.3	99.0 $\pm$ 1.7	0.6 $\pm$ 1.4	0.6 $\pm$ 1.4	158.4 $\pm$ 30.7
<sup>SH</sup> Air Optix	Lotrafilcon B	233.4 $\pm$ 33.9	99.9 $\pm$ 0.9	0.0 $\pm$ 1.1	0.0 $\pm$ 1.1	233.5 $\pm$ 33.1
<sup>SH</sup> Biofinity	Comfilcon B	122.8 $\pm$ 38.2	99.5 $\pm$ 1.4	0.2 $\pm$ 0.8	0.2 $\pm$ 0.8	123.1 $\pm$ 36.7
<sup>CH</sup> Biotrue	Nesofilcon A	155.5 $\pm$ 53.4	101.5 $\pm$ 0.7	-1.1 $\pm$ 0.1	-1.1 $\pm$ 0.1	153.4 $\pm$ 53.4
<sup>CH</sup> SofLens	Hilafilcon B	212.0 $\pm$ 83.8	100.2 $\pm$ 0.3	-0.2 $\pm$ 0.2	-0.2 $\pm$ 0.2	211.7 $\pm$ 84.1
<sup>CH</sup> Dailies AquaComfort Plus	Nelfilcon A	156.5 $\pm$ 14.5	101.4 $\pm$ 1.0	-1.0 $\pm$ 0.7	-1.0 $\pm$ 0.7	154.4 $\pm$ 15.4
<sup>CH</sup> 1-Day Acuvue Moist	Etafilcon A	96.5 $\pm$ 17.9	98.5 $\pm$ 1.0	0.7 $\pm$ 0.5	0.7 $\pm$ 0.5	98.0 $\pm$ 18.0

The concentration of the extracted drugs from the first extraction solution was determined by absorbance using the SpectraMax M5 UV-Vis spectrophotometer. The solution was diluted to the linear concentration ranges whenever necessary. The second and third extraction solutions were dried down using a nitrogen purge for approximately 1 hour. The extracted drugs were resuspended in 250  $\mu\text{L}$  methanol. Of this solution, 200  $\mu\text{L}$  was then pipetted into a 96-well UV-star microplate, and the samples were analyzed using the spectrophotometer.

### Statistical Analysis

Statistical analysis was performed using statistical software (Statistica 8; StatSoft, Tulsa, OK). All data are reported as mean  $\pm$  SD for  $n = 3$ . A repeated analysis of variance (ANOVA) was performed to determine the differences across extraction cycles. A 1-way ANOVA was used to determine the differences between lens types. Post-hoc Tukey multiple comparison tests were used when necessary. An unpaired  $t$ -test was used to compare the differences between the

uptake of drug between CH CLs and SH CLs. In all cases, statistical significance was considered significant for a value of  $P < 0.05$ . Graphs were plotted using software (GraphPad Prism 6; GraphPad, La Jolla, CA).

## Results

Tables 3–6 show the uptake of drugs on SH and conventional SH CLs incubated in a 1 mg/mL drug solution. Over 90% of total amount of extractable drug from the lenses was extracted with the first extraction cycle for most combinations of CL types and drugs tested ( $P < 0.001$ ; Figs. 1–4). For moxifloxacin and timolol, CH CLs absorbed more drug than SH CLs ( $P < 0.05$ ). There were no differences in drug uptake between CH CLs and SH CLs for natamycin and ketotifen ( $P > 0.05$ ).

For natamycin, the CLs with the highest and lowest drug uptake were hilafilcon B (211.7  $\pm$  84.1  $\mu\text{g}/\text{lens}$ ) and etafilcon A (98.0  $\pm$  18.0  $\mu\text{g}/\text{lens}$ ), respectively ( $P < 0.001$ ). For moxifloxacin, the CL

**Table 4.** Uptake of Moxifloxacin ( $\mu\text{g}$ ) on SH and CH CLs Incubated in a 1-mg/mL Drug Solution

Commercial Name	Material	Extraction 1, $\mu\text{g}$	Extracted, %	Extraction 2, $\mu\text{g}$	Extraction 3, $\mu\text{g}$	Total, $\mu\text{g}$
<sup>SH</sup> Pure Vision 2	Balafilcon A	45.3 $\pm$ 5.2	94.0 $\pm$ 3.2	1.2 $\pm$ 0.4	1.6 $\pm$ 1.4	48.1 $\pm$ 3.9
<sup>SH</sup> Acuvue Oasys	Senofilcon A	45.4 $\pm$ 11.1	90.2 $\pm$ 7.1	1.6 $\pm$ 2.1	2.9 $\pm$ 1.1	49.9 $\pm$ 8.2
<sup>SH</sup> Air Optix	Lotrafilcon B	43.0 $\pm$ 2.4	90.0 $\pm$ 1.0	2.4 $\pm$ 0.5	2.5 $\pm$ 0.4	47.8 $\pm$ 3.1
<sup>SH</sup> Biofinity	Comfilcon B	39.8 $\pm$ 5.7	89.5 $\pm$ 3.5	0.8 $\pm$ 0.2	4.0 $\pm$ 2.5	44.7 $\pm$ 7.5
<sup>CH</sup> Biotrue	Nesofilcon A	86.8 $\pm$ 9.0	97.5 $\pm$ 0.8	1.3 $\pm$ 0.9	1.0 $\pm$ 0.8	88.6 $\pm$ 9.3
<sup>CH</sup> SofLens	Hilafilcon B	101.8 $\pm$ 15.5	95.3 $\pm$ 0.9	2.8 $\pm$ 0.5	2.1 $\pm$ 0.6	106.7 $\pm$ 15.2
<sup>CH</sup> Dailies AquaComfort Plus	Nelfilcon A	69.6 $\pm$ 11.7	99.2 $\pm$ 2.2	0.2 $\pm$ 0.6	0.3 $\pm$ 1.4	70.1 $\pm$ 10.5
<sup>CH</sup> 1-Day Acuvue Moist	Etafilcon A	188.5 $\pm$ 9.7	94.7 $\pm$ 1.0	7.3 $\pm$ 2.7	3.3 $\pm$ 1.6	199.1 $\pm$ 8.3

**Table 5.** Uptake of Ketotifen ( $\mu\text{g}$ ) on SH and CH CLs Incubated in a 1-mg/mL Drug Solution

Commercial Name	Material	Extraction 1, $\mu\text{g}$	Extracted, %	Extraction 2, $\mu\text{g}$	Extraction 3, $\mu\text{g}$	Total, $\mu\text{g}$
<sup>SH</sup> Pure Vision 2	Balafilcon A	295.8 $\pm$ 4.7	94.7 $\pm$ 3.9	13.2 $\pm$ 4.5	3.9 $\pm$ 9.7	312.9 $\pm$ 15.9
<sup>SH</sup> Acuvue Oasys	Senofilcon A	248.8 $\pm$ 2.0	91.5 $\pm$ 0.3	9.5 $\pm$ 1.1	13.5 $\pm$ 1.3	271.9 $\pm$ 3.2
<sup>SH</sup> Air Optix	Lotrafilcon B	263.2 $\pm$ 4.0	94.2 $\pm$ 1.8	13.7 $\pm$ 0.6	2.7 $\pm$ 5.7	279.6 $\pm$ 6.3
<sup>SH</sup> Biofinity	Comfilcon B	250.4 $\pm$ 0.9	92.5 $\pm$ 1.4	14.3 $\pm$ 4.7	6.0 $\pm$ 7.9	270.7 $\pm$ 3.3
<sup>CH</sup> Biotrue	Nesofilcon A	218.0 $\pm$ 8.9	94.8 $\pm$ 2.6	3.4 $\pm$ 1.1	8.6 $\pm$ 5.1	230.0 $\pm$ 8.4
<sup>CH</sup> SofLens	Hilafilcon B	306.9 $\pm$ 6.4	92.6 $\pm$ 1.6	14.1 $\pm$ 3.3	10.5 $\pm$ 4.3	331.5 $\pm$ 10.7
<sup>CH</sup> Dailies AquaComfort Plus	Nelfilcon A	83.8 $\pm$ 2.7	98.2 $\pm$ 4.9	-0.8 $\pm$ 1.0	2.5 $\pm$ 5.2	85.5 $\pm$ 5.5
<sup>CH</sup> 1-Day Acuvue Moist	Etafilcon A	492.9 $\pm$ 10.4	92.6 $\pm$ 2.1	29.8 $\pm$ 9.3	9.7 $\pm$ 3.4	532.4 $\pm$ 14.3

with highest drug uptake was etafilcon A ( $199.1 \pm 8.3 \mu\text{g}/\text{lens}$ ), while comfilcon B had the lowest uptake ( $44.7 \pm 7.5 \mu\text{g}/\text{lens}$ ) ( $P < 0.001$ ). The highest drug uptake for ketotifen was for etafilcon A ( $532.4 \pm 14.3 \mu\text{g}/\text{lens}$ ), and the lowest was for nelfilcon A ( $85.5 \pm 5.5 \mu\text{g}/\text{lens}$ ) ( $P < 0.001$ ). Etafilcon A ( $79.1 \pm 13.3 \mu\text{g}/\text{lens}$ ) also had the highest uptake of timolol, while senofilcon A ( $32.4 \pm 9.5 \mu\text{g}/\text{lens}$ ) had the lowest uptake of the drug ( $P < 0.001$ ).

All CLs swelled in methanol during the extraction phase, with the exception of nelfilcon A, which shriveled. Pure CL extracts had high absorbance at wavelengths below 270 nm, so detection of drugs with lower absorbance wavelengths is unreliable with methanol extraction.

## Discussion

The objective of this study was to develop a simple direct method to quantify the amount of drug uptake in commercial CLs. Four drugs, natamycin, moxifloxacin, ketotifen, and timolol, were investigated.

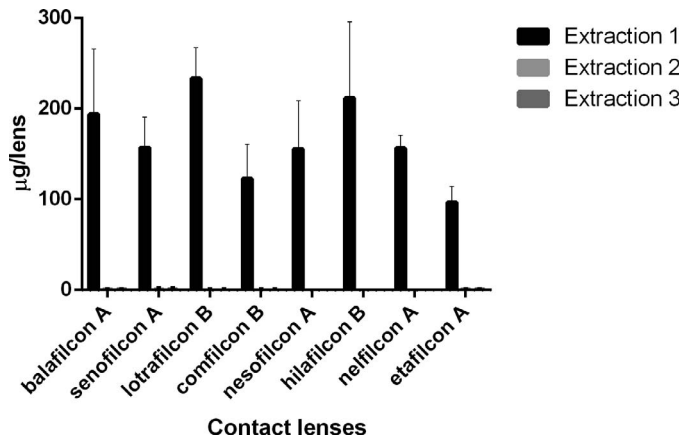
These drugs have been used to study a range of potential ocular therapies using CL drug delivery.<sup>3,6,8,16,38,40</sup> A simple extraction approach was developed using methanol as the extraction solvent. The method consists of incubating CLs in methanol for 2 hours to remove the bound drugs, and this was repeated for a total of three cycles.

For moxifloxacin and timolol, CH CLs absorbed more drugs than SH CLs ( $P < 0.05$ ). These results have been observed in previous studies with moxifloxacin.<sup>38,40</sup> There were no significant differences in uptake between CH CLs and SH CLs observed for natamycin and ketotifen fumarate ( $P > 0.05$ ), which are also similar to previously published results.<sup>6,8</sup>

Natamycin is an antifungal drug used to treat superficial fungal eye infections.<sup>41</sup> A previous study examined the uptake of natamycin in CH and SH hydrogels incubated in 20-mL suspension of 30  $\mu\text{g}/\text{mL}$  of drug (600  $\mu\text{g}/\text{vial}$ ).<sup>3</sup> The drug uptake, as measured indirectly by the concentration changes in the incubation solution, was between  $37.9 \pm 19.7$  and  $176.9 \pm 79.0 \mu\text{g}/\text{gel}$ .<sup>3</sup> These results are similar to those

**Table 6.** Uptake of Timolol ( $\mu\text{g}$ ) on SH and CH CLs Incubated in a 1-mg/mL Drug Solution

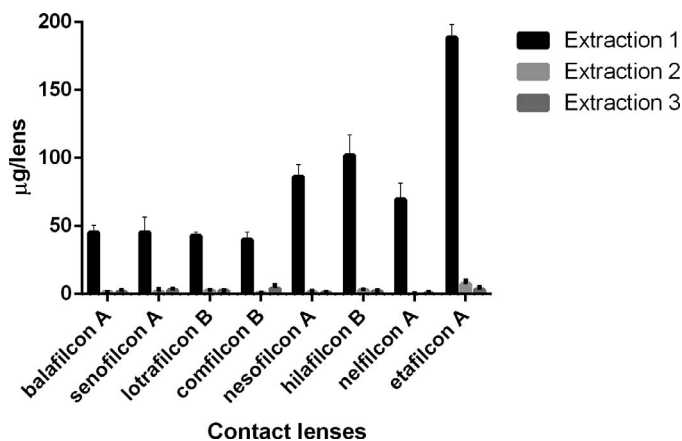
Commercial Name	Material	Extraction 1, $\mu\text{g}$	Extracted, %	Extraction 2, $\mu\text{g}$	Extraction 3, $\mu\text{g}$	Total, $\mu\text{g}$
<sup>SH</sup> Pure Vision 2	Balafilcon A	34.5 $\pm$ 4.9	92.4 $\pm$ 17.4	2.0 $\pm$ 7.7	1.3 $\pm$ 1.6	37.8 $\pm$ 4.2
<sup>SH</sup> Acuvue Oasys	Senofilcon A	28.1 $\pm$ 3.6	90.1 $\pm$ 21.1	4.3 $\pm$ 6.7	-0.1 $\pm$ 1.3	32.4 $\pm$ 9.5
<sup>SH</sup> Air Optix	Lotrafilcon B	27.6 $\pm$ 5.7	87.6 $\pm$ 14.0	4.0 $\pm$ 5.3	0.9 $\pm$ 0.2	32.5 $\pm$ 10.5
<sup>SH</sup> Biofinity	Comfilcon B	25.0 $\pm$ 3.2	88.3 $\pm$ 19.1	4.8 $\pm$ 5.7	-0.7 $\pm$ 0.3	29.2 $\pm$ 7.0
<sup>CH</sup> Biotrue	Nesofilcon A	36.3 $\pm$ 2.3	102.2 $\pm$ 13.3	0.7 $\pm$ 5.0	-1.1 $\pm$ 0.2	35.9 $\pm$ 5.4
<sup>CH</sup> SofLens	Hilafilcon B	50.2 $\pm$ 2.9	86.0 $\pm$ 2.3	7.1 $\pm$ 2.2	1.1 $\pm$ 0.9	58.5 $\pm$ 5.0
<sup>CH</sup> Dailies AquaComfort Plus	Nelfilcon A	33.3 $\pm$ 5.2	89.4 $\pm$ 21.1	4.2 $\pm$ 5.4	1.3 $\pm$ 3.5	38.9 $\pm$ 11.1
<sup>CH</sup> 1-Day Acuvue Moist	Etafilcon A	73.9 $\pm$ 10.3	03.7 $\pm$ 3.0	0.9 $\pm$ 3.3	4.4 $\pm$ 2.0	79.1 $\pm$ 13.3



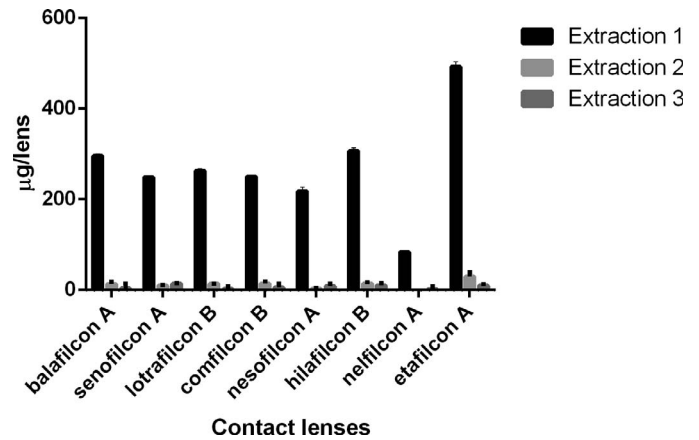
**Figure 1.** Natamycin ( $\mu\text{g}$ ) extracted from SH and CH CLs incubated in a 1-mg/mL drug solution.

obtained in this study when corrected for the total amount of natamycin in the incubation solution (current study: 1000  $\mu\text{g}/\text{vial}$ ), with total drug uptake between  $98.0 \pm 18.0$  and  $211.7 \pm 84.1$   $\mu\text{g}/\text{lens}$ .

Moxifloxacin is an important antimicrobial agent for treating a variety of ocular surface diseases.<sup>42</sup> The drug is very hydrophilic, so the majority of the drugs bound in the lenses should also be released subsequently in an aqueous medium. The release of moxifloxacin from commercial CLs incubated in a 1 mg/mL drug solution has been previously reported.<sup>38</sup> Nelfilcon A (Dailies AquaComfort Plus; Alcon) and etafilcon A (1-Day Acuvue Moist; Johnson & Johnson) released  $37 \pm 4$  and  $226 \pm 2$   $\mu\text{g}/\text{lens}$ , respectively.<sup>38</sup> These results are in fairly good agreement with the results obtained in this study for nelfilcon A ( $70.1 \pm 10.5$   $\mu\text{g}/\text{lens}$ ) and etafilcon A ( $199.1 \pm 8.3$   $\mu\text{g}/\text{lens}$ ).

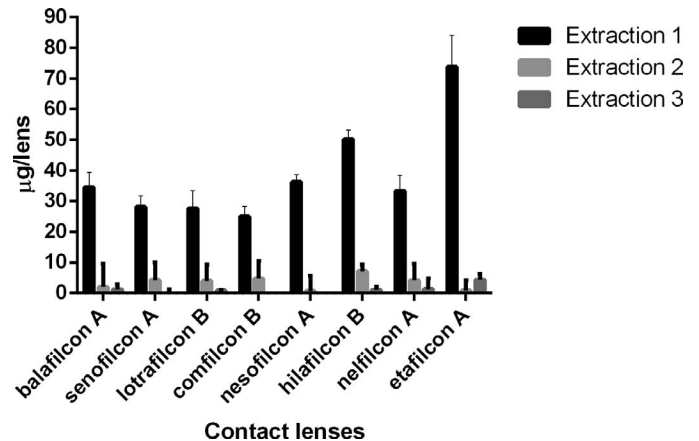


**Figure 2.** Moxifloxacin ( $\mu\text{g}$ ) extracted from SH and CH CLs incubated in a 1-mg/mL drug solution.



**Figure 3.** Ketotifen ( $\mu\text{g}$ ) extracted from SH and CH CLs incubated in a 1-mg/mL drug solution.

Ketotifen fumarate is a drug used to alleviate the signs and symptoms of seasonal allergic conjunctivitis.<sup>43</sup> A previous study reported the uptake of ketotifen fumarate in CLs incubated in 6 mL of 0.25 mg/mL (1250  $\mu\text{g}/\text{vial}$ ) ketotifen fumarate.<sup>8</sup> Six out of the eight CLs examined in the previous study were examined in this study. In general, the results for this study ( $85.5 \pm 5.5$  to  $532.4 \pm 14.3$   $\mu\text{g}/\text{lens}$ ) and the previous work ( $223.52 \pm 14.33$  to  $515.85 \pm 47.29$   $\mu\text{g}/\text{lens}$ )<sup>8</sup> are in very good agreement when corrected for the total amount of drug in the incubation solution. The only major difference between the two studies is the amount of drug uptake reported for nelfilcon A (Dailies AquaComfort Plus). Previously, the drug uptake for nelfilcon A was reported at  $223.52 \pm 14.33$   $\mu\text{g}/\text{lens}$ , with a total release of only  $40.36 \pm 14.33$   $\mu\text{g}/\text{lens}$ , or  $18.1\% \pm 1.4\%$ .<sup>8</sup> Considering that the drug release percentage for all the other lenses for that



**Figure 4.** Timolol ( $\mu\text{g}$ ) extracted from SH and CH CLs incubated in a 1-mg/mL drug solution.

particular study was between  $30.1\% \pm 5\%$  and  $61.7\% \pm 7.2\%$ , the amount of drug uptake for nelfilcon A may have been overestimated. The amount of drug uptake for nelfilcon A in this study at  $85.5 \pm 5.5 \mu\text{g}/\text{lens}$  would correspond more closely to the drug release previously published.

Timolol is a drug used to lower intraocular pressure for the treatment of glaucoma.<sup>44</sup> A previous study reported the uptake of timolol in 2 mL of 500  $\mu\text{g}/\text{mL}$  (1000  $\mu\text{g}/\text{vial}$ ) for poly-2-hydroxyethyl methacrylate (HEMA) CLs, a CH material, at  $113.58 \pm 1.54 \mu\text{g}/\text{lens}$ .<sup>31</sup> In comparison to the previous study, the amount of uptake for CH CLs in this study was slightly less, ranging between  $35.9 \pm 5.4 \mu\text{g}/\text{lens}$  and  $79.1 \pm 13.3 \mu\text{g}/\text{lens}$  of drug uptake for HEMA-containing lenses. The higher drug uptake previously reported could be attributed to the differences in the CL polymer. The commercial CLs tested in this study had a variety of other polymers in addition to HEMA, which could reduce the uptake of timolol maleate.

After the first extraction cycle for 2 hours in methanol, 90% of extractable drug was obtained for most combinations of lens types and drugs tested. Less than 10% of the total amount of extractable drugs was extracted in subsequent extraction cycles. This suggests that one extraction cycle at 2 hours with methanol is sufficient to estimate over 90% of the drug uptake in CLs. Thus, this method could provide a rapid and direct approach to quantify the amount of drug uptake in CLs. Two extraction cycles are sufficient to remove the majority of the drugs bound on the CLs. These extraction results are in consensus with other studies that quantify proteins and lipids from CLs using extraction methods.<sup>33–37</sup>

In theory, the extraction solvent should have a drug solubility equal to or higher than the release medium, should not react with the drug, should have a low boiling point so that it can be evaporated readily, and should be relatively inexpensive.<sup>45</sup> For these reasons, methanol was chosen as the extraction solvent for this study. Furthermore, methanol also has the effect of swelling the CLs, which helps facilitate the drug extraction process. With the exception of nelfilcon A, all lenses tested in this study swelled when exposed to methanol. For drugs insoluble in methanol, an alternative solvent that has high solubility for the drug of interest can be used. The selection of the right solvent is important in ensuring a high extraction efficiency of the drug from the CL.

Indirect methods that measure the changes in the

concentration of the drug-loading solution are subjected to various inaccuracies, such as drug precipitation or deposition onto vials, which can overestimate the amount of drug uptake. Furthermore, to measure small changes in a high drug-loading solution requires very sensitive instrumentation and precise handling and sample preparation, which potentially increase the errors with measurements. Unlike previous indirect approaches, this extraction method measures drug uptake directly from the CL. This method can also be modified, such as increasing the extraction time, increasing the cycles of extractions, or changing the extraction solvent as necessary to better suit other drug and CL combinations.

There are limitations that should be noted using this approach. First, methanol as an extraction solvent has an effect of also extracting other components from the CL polymer due to its swelling effect. As a result, depending on the CL properties, the lens extracts may cause spectral interferences. Consequently, a negative control with only the lens extracts for each CL type should be used as the background. The interference problem can be solved by using more advanced analytical methods based on multicomponent analysis or using high-performance liquid chromatography to separate the samples prior to UV spectrometry.

The second limitation is that, unlike the indirect approach in which the same lenses are used in both the uptake study and the release study, this approach requires two sets of lenses. The set of lenses measured for the uptake study is not the same as the one used for the release study. Consequently, experimental conditions for uptake and release studies need to be the same to ensure comparable results.

The results of this study suggest that both indirect and direct approaches to measuring drug uptake in CLs provide comparable results. However, in cases where the concentrations of the drug-loading solution are very high or when the amounts of drugs released from the lens are relatively low, the direct approach may provide a better estimate of drug uptake. Furthermore, the direct approach is less sensitive to errors with instrumentation, sample preparation, and handling. For a simple and rapid estimate of the drug uptake in a CL in this study, a 2-hour methanol extraction of the CL after the drug incubation period was sufficient. Future studies will examine alternative extraction solvents to measure the uptake of other drugs on CLs.

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